

**HIGHLIGHTS OF PRESCRIBING
INFORMATION**

These highlights do not include all the information needed to use Flublok[®] safely and effectively. See full prescribing information for Flublok.

Flublok (Influenza Vaccine)

Sterile Solution for Intramuscular Injection

2012-2013 Formula

Initial U.S. Approval: 2013

-----INDICATIONS AND USAGE-----

Flublok is a vaccine indicated for active immunization against disease caused by influenza virus subtypes A and type B contained in the vaccine. Flublok is approved for use in persons 18 through 49 years of age. (1)

-----DOSAGE AND ADMINISTRATION-----

A single 0.5 mL dose for intramuscular injection. (2)

-----DOSAGE FORMS AND STRENGTHS-----

A sterile solution for injection supplied in 0.5mL single dose vials. (3)

-----CONTRAINDICATIONS-----

Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine.

-----WARNINGS AND PRECAUTIONS-----

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of potential benefits and risks. (5.1)

-----ADVERSE REACTIONS-----

In adults 18 through 49 years of age, the most common ($\geq 10\%$) injection-site reaction was pain ($>37\%$); the most common ($\geq 10\%$) solicited systemic adverse reactions were headache ($>15\%$), fatigue ($>15\%$) and myalgia ($>11\%$). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Protein Sciences Corporation at 1-888-855-7871 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

-----USE IN SPECIFIC POPULATIONS-----

- Safety and effectiveness of Flublok have not been established in pregnant women, nursing mothers, children, or adults 50 years of age and older. (8.1, 8.3, 8.4, 8.6)
- A pregnancy registry is available for Flublok. Contact: Protein Sciences Corporation by calling 1-888-855-7871. (8.1)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Flublok is a vaccine indicated for active immunization against disease caused by influenza virus subtypes A and type B contained in the vaccine. Flublok is approved for use in persons 18 through 49 years of age.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage

Administer Flublok as a single 0.5-mL dose.

2.2 Administration

Shake the single-dose vial gently before withdrawing the vaccine dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permits. If either of these conditions exists, the vaccine should not be administered.

The preferred site for injection is the deltoid muscle. Administration is by sterile needle and syringe.

Flublok should not be mixed with any other vaccine in the same syringe or vial.

3 DOSAGE FORMS AND STRENGTHS

Flublok is a sterile solution supplied in single-dose vials, 0.5 mL.

4 CONTRAINDICATIONS

Flublok is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis), to any component of the vaccine (see *Description* [11]).

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an increased frequency of GBS. Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than one additional case per 1 million persons vaccinated. If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of the potential benefits and risks.

5.2 Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

5.3 Altered Immunocompetence

If Flublok is administered to immunocompromised individuals, including persons receiving immunosuppressive therapy, the immune response may be diminished.

5.4 Limitations of Vaccine Effectiveness

Vaccination with Flublok may not protect all vaccine recipients.

6 ADVERSE REACTIONS

The most common ($\geq 10\%$) injection-site reaction was pain ($>37\%$); the most common ($\geq 10\%$) solicited systemic adverse reactions were headache ($>15\%$), fatigue ($>15\%$) and myalgia ($>11\%$).

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a vaccine cannot be directly compared to rates in the clinical studies of another vaccine and may not reflect the rates observed in clinical practice.

Flublok has been administered to and safety data collected from 2497 adults 18 through 49 years of age enrolled in two randomized, placebo-controlled clinical trials (1, 2). In both studies local (injection site) and systemic adverse reactions were solicited with the use of a memory aid for 7 days following vaccination. Unsolicited adverse reactions were collected for 28 days post-vaccination and Serious Adverse Events (SAEs) were collected for 6 months post-vaccination via clinic visit or telephone follow up on Day 28, telephone follow up on Day 180, or by spontaneous reporting.

In a clinical trial (Study 1, Table 1) that included 2,344 subjects randomized to receive Flublok and 2,304 subjects randomized to receive saline placebo, the mean age of participants was 32.5 years, 59% were female, and 67% were Caucasian (see Clinical Studies (14)).

Table 1: Frequency of Solicited Injection Site Reactions and Systemic Adverse Reactions within 7 Days of Administration of Flublok or Placebo in Adults 18-49 Years of Age, Study 1, Total Vaccinated Cohort^{1,2,3}

	Flublok N=2272	Placebo N=2231
Local Adverse Reactions	%	%
Pain	37	8
Redness	4	2
Swelling	3	2
Bruising	3	3
Systemic Adverse Reactions	%	%
Headache	15	16
Fatigue	15	14
Muscle Pain	11	7
Fever [‡]	<1	<1
Joint pain	4	4
Nausea	6	5
Chills	3	3

NOTE: Data based on the most severe response reported by subjects. Results >1% reported to nearest whole percent; results >0 but <1 reported as <1%.

[‡] Fever defined as $\geq 99.8^{\circ}\text{F}$ (37.7°C).

¹ Total Vaccinated Cohort is defined as all randomized subjects who received study vaccine according to the treatment actually received and who provided data.

² Study 1 is registered as NCT00539981 under the National Clinical Trials registry.

³ Denominators for Study 1: The total number of enrolled subjects was 2344 in the Flublok group and 2304 in the placebo group. For all categories except fever, the number of subjects with missing values was 72 in the Flublok group and 73 in the Placebo group so that these denominators are 2272 and 2231 respectively. For fever, 89 Flublok recipients and 104 Placebo recipients were missing data, making these denominators 2255 and 2200 respectively.

Across trials, through 6 months post vaccination, two deaths were reported, one in a Flublok recipient and one in a placebo recipient. Both deaths occurred more than 28 days following vaccination and neither was considered vaccine-related. SAEs were reported by 32 Flublok recipients and 35 placebo recipients. One SAE in a Flublok recipient was assessed as possibly related to the vaccine: pleuropericarditis with effusions requiring hospitalization and drainage. No specific cause was identified. The patient recovered.

In Study 1, the most frequent unsolicited adverse events, occurring in 1%-2% of subjects, were nasopharyngitis, upper respiratory infection, headache, cough, nasal congestion, pharyngolaryngeal pain, and rhinorrhea.

6.2 Postmarketing Experience

No postmarketing safety data are available for Flublok.

7 DRUG INTERACTIONS

Data evaluating the concomitant administration of Flublok with other vaccines are not available.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in rats at a dose approximately 300 times the human dose (on a mg/kg basis) and have revealed no evidence of impaired fertility or harm to the fetus due to Flublok. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this vaccine should be used during pregnancy only if clearly needed. The effect of Flublok on embryo-fetal and pre-weaning development was evaluated in pregnant rats. Animals were administered Flublok by intramuscular injection twice prior to gestation and once during the period of organogenesis (gestation days 6), 0.5 ml/rat/occasion (approximately 300-fold excess relative to the projected human dose on a mg/kg basis). No adverse effects on mating, female fertility, pregnancy, parturition, lactation, embryo-fetal and pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

8.3 Nursing Mothers

Flublok has not been evaluated in nursing mothers. It is not known whether Flublok is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Flublok is administered to a nursing woman.

8.4 Pediatric Use

Data from a randomized, controlled study demonstrated that children 6 months to less than 3 years of age had diminished hemagglutinin inhibition (HAI) responses to Flublok as compared to a U.S.-licensed influenza vaccine approved for use in this population, strongly suggesting that Flublok would not be effective in children younger than 3 years of age. Safety and effectiveness of Flublok in children 3 years to less than 18 years of age have not been established.

8.5 Geriatric Use

The safety and effectiveness of Flublok have not been established in persons 50 years of age and older.

11 DESCRIPTION

Flublok [Influenza Vaccine] is a sterile, clear, colorless solution of recombinant hemagglutinin (HA) proteins from three influenza viruses for intramuscular injection. It contains purified HA proteins produced in a continuous insect cell line (*expresSF+*[®]) that is derived from Sf9 cells of the fall armyworm, *Spodoptera frugiperda*, and grown in serum-free medium composed of chemically-defined lipids, vitamins, amino acids, and mineral salts. Each of the three HAs is expressed in this cell line using a baculovirus vector (*Autographa californica* nuclear polyhedrosis virus), extracted from the cells with Triton X-100 and further purified by column chromatography. The purified HAs are then blended and filled into single-dose vials.

Flublok is standardized according to United States Public Health Service (USPHS) requirements. For the 2012 - 2013 influenza season it is formulated to contain 135 mcg HA per 0.5 mL dose, with 45 mcg HA of each of the following 3 influenza virus strains: A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2), and B/Wisconsin/1/2010.

A single 0.5 mL dose of Flublok contains sodium chloride (4.4 mg), monobasic sodium phosphate (0.195 mcg), dibasic sodium phosphate (1.3 mg), and polysorbate 20 (Tween[®] 20) (27.5 mcg). Each 0.5 mL dose of Flublok may also contain residual amounts of baculovirus and host cell proteins (≤ 28.5 mcg), baculovirus and cellular DNA (≤ 10 ng), and Triton X-100 (≤ 100 mcg).

Flublok contains no egg proteins, antibiotics, or preservatives. The stoppers used for the single-dose vials do not contain latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Flublok contains recombinant HA proteins of the three strains of influenza virus specified by health authorities for inclusion in the annual seasonal vaccine. These proteins function as antigens which induce a humoral immune response, measured by hemagglutinin inhibition antibody (HAI).

Antibodies against one influenza virus type or subtype confer limited or no protection against another. Furthermore, antibodies to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual replacement of one or more influenza virus strains in each year's influenza vaccine. Therefore, influenza vaccines are standardized to contain the hemagglutinins of influenza virus strains (i.e., typically two type A and one type B), representing the influenza viruses likely to be circulating in the U.S. in the upcoming winter.

13 NONCLINICAL TOXICOLOGY

Flublok has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals.

Reproduction studies performed in female rats revealed no evidence of impaired fertility due to Flublok (see Pregnancy 8.1).

14 CLINICAL STUDIES

Efficacy Against Culture-Confirmed Influenza

The efficacy of Flublok was evaluated in a randomized, observer-blind, placebo-controlled multicenter trial conducted in the U.S. during the 2007-2008 influenza season (Study 1). The study enrolled and vaccinated 4648 healthy adults (mean age 32.5 years) randomized in a 1:1 ratio to receive a single dose of Flublok (n=2344) or saline placebo (n=2304). Among enrolled subjects, 59% were female, 67% were white, 19% African-American, 11% Latino/Hispanic, 2% Asian and < 1% other. The two groups were similar in demographics. Culture-confirmed influenza was assessed by active and passive surveillance for influenza-like illness (ILI) beginning 2 weeks post-vaccination until the end of the influenza season, approximately 7 months post- vaccination. ILI was defined as having at least 2 of 3 symptoms (no specified duration) in the following categories: 1) fever $\geq 100^{\circ}\text{F}$; 2) respiratory symptoms (cough, sore throat, runny nose/stuffy nose); or 3) systemic symptoms (myalgias, arthralgias, headache, chills/sweats, tiredness/malaise). For subjects with an episode of ILI, nasal and throat swab samples were collected for viral culture.

The primary efficacy endpoint was Centers for Disease Control-defined influenza-like illness (CDC-ILI) with a positive culture for an influenza virus strain antigenically resembling a strain represented in Flublok. CDC-ILI is defined as fever of $\geq 100^{\circ}\text{F}$ oral accompanied by cough, sore throat, or both on the same day or on consecutive days (1). Attack rates and vaccine efficacy (VE), defined as the relative reduction in the influenza rate for Flublok relative to placebo, were calculated for the total vaccinated cohort (n=4,648). The pre-defined success criterion for the primary efficacy analysis was that the lower bound of the 95% confidence interval (CI) of VE should be at least 40%. Vaccine efficacy against antigenically matched culture-confirmed CDC-ILI could not be determined reliably because 96% of the influenza isolates obtained from subjects in Study 1 were not antigenically matched to the strains represented in the vaccine. An exploratory analysis of VE of Flublok against all strains regardless of antigenic match isolated from any subject with an ILI, not necessarily CDC-defined ILI, demonstrated an efficacy estimate of 44.8% (95% CI 24.4, 60.0). See Table 2 for a presentation of VE by case definition and antigenic similarity.

Table 2: Vaccine Efficacy Against Culture-Confirmed Influenza in Healthy Adults 18-49 Years of Age, Study 1*

Years of Age, Study 1

Case definition	Flublok (N=2344)		Saline Placebo (N=2304)		Flublok Vaccine Efficacy ¹ , %	95% Confidence Interval
	Cases, n	Rate, %	Cases, n	Rate, %		
Positive culture with a strain represented in the vaccine						
CDC-ILI, all matched strains ^{2,3}	1	0.04	4	0.2	75.4	(-148.0, 99.5)
Any ILI, all matched strains ^{4,5}	2	0.1	6	0.3	67.2	(-83.2, 96.8)
Positive culture with any strain, regardless of match to the vaccine						
CDC-ILI, all strains ^{2,6}	44	1.9	78	3.4	44.6	(18.8, 62.6)
Sub-Type A	26	1.1	56	2.4	54.4	(26.1, 72.5)
Type B	18	0.8	23	1.0	23.1	(-49.0, 60.9)
Any ILI, all strains ⁴	64	2.7	114	4.9	44.8	(24.4, 60.0)
Sub-Type A	41	1.7	79	3.4	49.0	(24.7, 65.9)
Type B	23	1.0	36	1.6	37.2	(-8.9, 64.5)
*In Study 1 (NCT00539981) vaccine efficacy analyses were conducted on the Total Vaccinated Cohort (all randomized subjects who received study vaccine according to the treatment actually received and who provided data). Vaccine efficacy (VE) = 1 minus the ratio of Flublok/placebo infection rates.						
¹ Determined under the assumption of Poisson event rates, according to Breslow and Day, 1987.						
² Meets CDC influenza-like illness (CDC-ILI) defined as fever of ≥100°F oral accompanied by cough and/or sore throat, on the same day or on consecutive days.						
³ Primary endpoint of study.						
⁴ All culture-confirmed cases are considered, regardless of whether they qualified as CDC-ILI.						
⁵ Secondary endpoint of study.						
⁶ Exploratory (prespecified) endpoint of study.						

15 REFERENCES

1. Treanor JJ, El Sahly HM, King J, et al. Protective efficacy of a trivalent, insect cell-expressed, recombinant hemagglutinin protein vaccine (FluBlok) against culture confirmed influenza in healthy adults: a randomized, placebo-controlled trial. *Vaccine*, 2011, Vol. 13, 29, pp. 7733-7739.
2. Treanor JJ, Schiff GM, Hayden FG, et.al. Safety and immunogenicity of a baculovirus-expressed hemagglutinin influenza vaccine: a randomized controlled trial. *JAMA*. 2007, Vol. 297, pp. 1577-1582.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Flublok is supplied as a single-dose, 0.5 mL vial in a 10 vial carton:

Presentation	Carton NDC Number	Components and NDC Number
Single-Dose Vial	42874-012-10	Ten 0.5 mL single-dose vials [NDC 42874-012-01]

16.2 Storage and Handling

- Store refrigerated between 2° and 8°C (36° and 46°F).
- Do not freeze. Discard if product has been frozen.
- Protect vials from light
- Do not use after expiration date shown on the label.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information Sheet).

Inform the vaccine recipient of the potential benefits and risks of vaccination with Flublok.

Inform the vaccine recipient that:

- Flublok contains non-infectious proteins that cannot cause influenza.
- Flublok stimulates the immune system to produce antibodies that help protect against influenza viruses contained in the vaccine, but does not prevent other respiratory infections.

Instruct the vaccine recipient to report any adverse events to their healthcare provider and/or to the Vaccine Adverse Event Reporting System (VAERS).

Provide the vaccine recipient with the Vaccine Information Statements which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to vaccination. These materials are available free of charge at the Centers for Disease Control (CDC) website (www.cdc.gov/vaccines).

Inform the vaccine recipient that safety and efficacy have not been established in pregnant women. Register women who receive Flublok while pregnant in the pregnancy registry by calling 1-888-855-7871.

Instruct the vaccine recipient that annual vaccination to prevent influenza is recommended.

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